UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

VB

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/184,572	11/02/98	MCKERRACHER L	99999/MARUSY

EXAMINER	
TURNER, S	
ART UNIT	**PAPER NUMBER**
1644	11

HM12/0607

WILLIAM J HONE
FISH & RICHARDSON
SUITE 2800
45 ROCKEFELLER PLAZA
NEW YORK NY 10111

DATE MAILED: 06/07/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

U.S. G.P.O. 1999 460-693

Office Action Summary

Application No.	Applicant(s)
09/184,572	McKerracher et al
Examiner	**Group Art Unit**
Sharon L. Turner, Ph.D.	1644

☒ Responsive to communication(s) filed on 2-13-00

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 22-31 is/are pending in the applicat

Of the above, claim(s) 25-29 is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 22-24, 30, and 31 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 7

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The Group and/or Art Unit of U.S. Patent application SN 09/184,572 has changed. In order to expedite the correlation of papers with the application please direct all future correspondence to Examiner Turner, Technology Center 1600, Art Unit 1644.

2. The executed oath submitted 4-19-99 serves to correct the earlier identification of inventorship in accordance with 37 CFR 1.48(f).

Priority

3. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Canada on 10-31-97. It is noted, however, that applicant has not filed a certified copy of the 2.214.841 application as required by 35 U.S.C. 119(b). Prior Art is applied accordingly.

Election/Restriction

4. Applicant's election with traverse of Group I, claims 22-24 and 30-31, species ADP-ribosyl transferase C3 antagonist, in Paper No. 10, filed 2-22-00 is acknowledged. The traversal is on the ground(s) that applicants have demonstrated that inactivation of Rho family members by Rho antagonists permits neurite outgrowth and allows neurite extension in the presence of growth inhibitory factors, that this in turn can foster the regrowth of injured or degenerating neurons in the peripheral or central nervous system, that the claims are directed towards a single

invention, and that the group of candidate Rho antagonists are optional embodiments of the singular method of the invention.

This is not found persuasive because the products and methods are distinct as set forth in the restriction requirement and the Rho antagonists differ in both structural and functional characteristics such that the claimed methods of treatment with the Rho antagonists do not overlap. A search of the prior art for one of the antagonist would not reveal prior art for any other antagonist. In addition, a prior art finding for one Rho antagonist molecule would not render another obvious under 35 USC 103, and thus the species are distinct within the claimed methods.

The requirement is still deemed proper and is therefore made FINAL.

5. Claims 25-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 22-24 and 30-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey

to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification discloses proteins named ADP-ribosyl transferase C3 enzyme, Rho, A-37 and Y-27632 which correspond to various chemical, and polypeptide structures. The claims are directed to or encompass Rho antagonists and Rho-family antagonists including chimeric proteins, analogs, derivatives, and mutants which are not described in the specification by name, structure or function. Thus, none of these compounds meet the written description provision of 35 USC 112, first paragraph.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is for purposes of the 'written description' inquiry, whatever is now claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed compounds and peptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The specific nucleic and amino acids are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, the full breadth of claims fails to meet the written description provision of 35 USC 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

8. Claims 22-24 and 30-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of overcoming axonal growth inhibition from chemorepulsive factors in a central nervous system or a peripheral nervous system of a subject, the method comprising delivering ADP-ribosyl C3 transferase to said CNS or PNS wherein said delivering promotes increased outgrowth of damaged neuronal axons, does not reasonably provide enablement for neuronal regeneration, outgrowth induced by any Rho antagonist or Rho mutant, or dendritic outgrowth. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

As to claims 22-24 and 30-31, the skilled artisan recognizes that even single amino acid mutations may affect the biological function of proteins in an unpredictable manner, see in particular Choh, PNAS, 77(6):3211-14, June 1980. The claims recite rho antagonists which are

mutants, derivatives, chimeric proteins and active fragments. However, the specification fails to teach the breadth of Rho antagonists which retain the ability to overcome chemorepulsive factors. For example, there are no required residues, conformational epitopes, conserved immunoreactivity, structure or functional activities which define the ability to act as a rho antagonist. In addition, antagonists may be specific to a certain rho-family member, such as C3 transferase is specific to Rho, see in particular Jin et al., 1997 (IDS), p. 6528, column 2, lines 36-39. The nature of the invention is complex as chemorepulsive factors may be differentially expressed in the CNS in comparison to the PNS, different cells and anatomical locations are affected differently upon, damage and the type and extent of damage in the CNS and PNS is dependent upon multiple factors including but not limited to the blood supply, the presence or absence of pathogenic organisms, the presence or absence of schwann cells, microglia and macrophages, the prevalence of complicating factors, for example the presence Alzheimer's plaques and the presence of one or more chemorepulsive factors.

As to claims 22-24 and 30-31, evidence suggests that Rho-family mutants differentially affects axons, dendritic trunks and spines, see in particular Luo et al., 1994 and Luo et al., 1996 (IDS) which teach that mutations in Drac1 and Rac1 inhibit axonal outgrowth but not of dendrite outgrowth. Thus, it appears that specific Rho family members and Rho antagonists differentially affect axonal and dendritic neuronal outgrowth. The examples provided by the instant specification are restricted to a teaching that following optic nerve crush, animals exhibited greater *axonal* outgrowth when administered C3 transferase, a Rho-specific antagonist. Thus, the

specifications enablement appears to be limited to producing increased *axonal* outgrowth following treatment with C3 transferase.

In addition, with regard to claims 22-24 and 30-31, the sum affect of promoting neurite outgrowth is dependent upon the particular chemorepulsive factor, the Rho-family member affected and the specific Rho antagonist. For example, as set forth above the inhibitor C3 transferase is not known to affect other Rho-family members. Jin et al., 1994 (IDS) also teach that dominant negative Rac1 inhibits collapsin-1-induced collapse of growth cones and collapsin-1 inhibition of neurite outgrowth but that dominant negative Rac1 remains sensitive to myelin-induced growth. Further, a similar mutant of cdc42 does not alter growth cone structure, neurite elongation or collapsin-1 sensitivity. Thus, it appears that the Rho family member, antagonist and chemorepulsive factor are critical for neuronal outgrowth. However, the specification provides no guidance such that the artisan would expect that other rho-family antagonists may produce such effects following nerve crush. There is no guidance as to the Rho-family members present at the injury site and there is no guidance as to the chemorepulsive factors which are present following damage in optic nerve crush, the CNS or PNS. Thus, the specifications enablement appears to be restricted to promoting axonal outgrowth following optic nerve crush by delivering C3 transferase.

The specification does not teach *neuronal* regeneration, i.e., the regeneration of new neuronal cells but alternatively appears to teach *axonal* outgrowth. The skilled artisan recognizes that neuronal cells do not regenerate following embryogenesis. In additon, there are multiple

factors in particular to mammals which lead to the intrisic property that CNS neurons fail to regenerate following transection, in particular as taught by Jackowski, Br. J. of Neurosurgery, 9:303-317, 1995, see in particular abstract and p. 304-313. Applicants demonstration fails to teach regeneration because the neuronal axons are not repaired, i.e., they do not traverse the transection to establish functional connections with the severed partner. Thus, the scope of applicants enablement appears to be restricted to increased axonal outgrowth.

Further, with respect to the limitation of claim 23 wherein the damaged neurons result from spinal cord injury, stroke, or neurodegenerative disorders, the specification is limited to the teaching of overcoming growth inhibition from chemorepulsive factors in the CNS or PNS. The specification does not teach that spinal cord injury, stroke or neurodegenerative diseases are associated with chemorepulsive factors. The specification is limited to the demonstration of promoting axonal outgrowth following nerve crush. As taught by McKerracher et al., Exp. Opin. Ther. Patents, 1999, 9(11):1571-74, p. 1573, paragraph spanning columns 1-2, the "suggested use of Rho antagonists in neurodegenerative diseases seems to be based on the assumption that neurodegeneration is associated with increased concentrations of nerve-growth inhibitory factors. This is not necessarily true; indeed there are data from studies of the AD brain which indicate a loss of growth-inhibitory activity in both aqueous and lipid soluble extracts." Thus, as the specification does not disclose the diseases or injuries which are associated with increased nerve-growth inhibitory factors, the scope of enablement cannot be extended to specific diseases which

are not known to be associated with increased nerve-growth inhibitory factors and which are not known to have overcome growth inhibition via Rho antagonists.

Thus, in view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue experimentation to make and use the claimed invention.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 22-24 and 30-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite "Rho antagonists" and "Rho-family antagonists."

In claims 22-24 and 30-31, the metes and bounds of a Rho antagonist or a Rho-family antagonist are unclear because the skilled artisan is not readily apprised of the molecules encompassed by the claim. The metes and bounds of the "Rho-family" is unclear. The specification fails to teach which proteins are encompassed by "Rho" and a "Rho-family member." There exists no defined structural or functional limitation such that the proteins is recognized. Further, there is no defined structure or function of a Rho antagonist. Thus, not only is the artisan unsure of the antagonists encompassed, but without direction as to that which is encompassed by Rho or a Rho-family member, one of skill in the art can not determine that which is encompassed by a rho antagonist or a rho family antagonist.

In claim 24, A-37 and Y-27632 are unclear as there are no structural or functional features of the claimed compounds. The chemical compositions should be recited and distinguished from the names.

In claims 22-24 and 30-31, the metes and bounds of "promoting regeneration" and "damaged neurons" is unclear because the skilled artisan has no guidance as to the effects produced via "promoting regeneration" and cannot readily recognize whether a neuronal cell is "damaged." There does not appear to be an assay for functional regeneration or particular condition with which the method is associated. Thus, the metes and bounds of the method are unclear and the artisan is not readily apprised of when the invention has been practiced.

Claim Rejections - 35 USC § 102 or 103

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 22, 24 and 30-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Somlyo, Nature 389:908-911 (IDS).

Somylo teach the administration of Y-27632 a Rho-associated kinase inhibitor which when administered to animals reduces high blood pressure. The administration of the compound to animals inherently produces the promotion of regeneration of damaged neurons. The

the inhibition of neuronal axon growth associated with growth inhibitory proteins including myelin and glial scar. Thus, the reference teachings anticipate the claimed invention as the method merely comprises administration of the compound which is equivalent to Somylos teaching of administration for high blood pressure. The blood stream would deliver the compound to both the CNS and the PNS and there appears to be no measurable effect to promoting regeneration.

13. Claims 22, 24 and 30-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Zipkin et al., Cell, 90:883-894, 1997 (IDS).

Zipkin et al teach mig2 mutants which are defective in GTP hydrolysis, see in particular, p. 883, column 2, lines 30. The mutants direct neuronal axon outgrowth, see in particular gm38, Table 1. These neurons are within the PNS and CNS of C. elegans and occur in the presence of myelin and glia. The neurons are damaged as they are mutated for mig2. Thus, the reference teachings anticipate the claimed invention. Thus, the reference teachings anticipate the claimed invention.

14. Claims 22-24 and 30-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Bartsch et al., Neuron, 15:1375-81, 1995.

Bartsch et al teach increased axonal regrowth following optic nerve crush in wild-type and MAG-deficient mice after application of the IN-1 antibody directed against the neurite growth inhibitors NI-35 and NI-250. The treatment inherently possess the property of preventing

GTP exchange. The injury is associated with glial and myelin scar. Thus, the reference teachings anticipate the claimed invention.

15. Claims 22-24 and 30-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Zalish et al., Retina, 13:145-47, 1993.

Zalish teach attenuation of axonal loss following optic nerve crush via treatment with gangliosides which inherently prevents GTP exchange. The treatment thus results in increased axonal regeneration of neurons as measured by increased vialble axons 2 mm distal to the injury site 2 and 4 weeks following monosialogangliosides. The injury is associated with glial and myelin scar formation at the site of the injury. Thus, the reference teachings anticipate the claimed invention.

16. Claims 22, 24 and 30-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Dillon et al., Methods in Enzymol., 256:174-95, 1995.

Dillon et al., teach C3 transferase assay in brain homogenates which comprise the administration of C3 transferase to neuronal cells of the CNS of a subject, the CNS being associated with glia and myelin. The administration of 40 ug/ml recombinantly purified C3 inherently promotes neuronal regeneration and reverses inhibition by growth inhibitory proteins in the mammalian CNS. The tissue inherently contains glial and myelin scars. Thus, the reference teachings anticipate the claimed invention.

Status of Claims

17. No claims are allowed.

18. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (703) 308-3973.

Sharon L. Turner, Ph.D.
June 5, 2000

Christina Chan

CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
GROUP ~~1800~~ 1640